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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,650	WEINER ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14-17,19,38,55-60,64,66-71,75 and 77* is/are pending in the application.

4a) Of the above claim(s) *38,64 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,14-17,19,55-60,66-71 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/31/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

As stated in the notice of non-compliant amendment mailed on 10/12/2010, the finality of the office action mailed on 01/22/2010 is withdrawn in view of the pre-appeal conference decision mailed on 08/09/2010. The decision is in response to Applicant's pre-appeal conference request filed on 06/22/2010. Prosecution on the merits resumes.

Applicant's claim amendments filed on 11/12/2010 have been entered.

Claims 2-13, 18, 20-37, 39-54, 61-63, 65, 72-74, and 76 are cancelled. Claim 77 is amended.

Claims 1, 14-17, 19, 38, 55-60, 64, 66-71, 75, and 77 are pending.

It is noted that as Applicant elected "cytokine" as the species recited in claim 1 and "IL-15" as the species recited in claim 77 in the reply filed on 11/09/2010. Accordingly, claims 38, 64, and 75 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 14-17, 19, 55-60, 66-71 and 77 are currently under examination to the extent of elected species, cytokine IL-15.

This application, 10/560,650, is a 371 of PCT/US04/18962 filed on 06/14/2004, which claims benefit of provisional application 60/478,205 filed on 06/13/2003 and claims benefit of provisional application 60/478,210 filed on 06/13/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Previous rejection of claims 66 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is **withdrawn** because Applicant's arguments in light of claim amendments filed on 03/22/2010 and 11/12/2010 have been fully considered and found persuasive. The withdrawal of this rejection has been documented in the advisory action mailed on 04/07/2010.

For the clarity of record, Applicant's statements filed on 03/22/2010 are cited below.

The limitation of non-IgE protein in claim 66 applies to the non-IgE protein in claim 1. While claim 1 itself includes two alternative limitations, i.e. a non-IgE protein from the same species as the IgE signal peptide or a non-IgE protein that is one of several expressly recited immunomodulatory proteins, the additional limitation in claim 66 is clear in indicating that the non-IgE protein that is from the same species as the IgE signal peptide is an immunomodulatory protein or the non-IgE protein is one of several expressly recited immunomodulatory proteins without limitation to whether or not it is from the same species. Claim 66 is clear and definite.

Claim 77 has been rejected as being indefinite due to the inclusion of certain repetitive language. The objected to language was included due to an obvious typographical error and has been deleted by the amendment. As amended, claim 77 is clear and definite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Previous scope of enablement rejection of claims 21-23, 54, 61-63, 65, 72-74, and 76 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising an isolated nucleic acid molecule, wherein the isolated nucleic acid molecule comprises a nucleic acid sequence consisting of a nucleic acid sequence that encodes a

fusion protein that consists of either a non-IgE protein or an immuno-modulating protein sequence linked to an IgE signal peptide, does not reasonably provide enablement for (1) any pharmaceutical composition or (2) any DNA vaccine for generation of a protective immunity against the infection of a pathogen or against the development of a disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, is **moot** because the claims have been cancelled, which has been documented in the advisory action mailed on 04/07/2010.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Previous rejection of claims 1, 14-17, 19, 21-23, 54-63, 65-74, and 76 under 35 U.S.C. 102(a) and 102(e) as being anticipated by Weiner et al. (US 2002/0123099, A1, Publication date Sep. 5, 2002) is **withdrawn** because upon further consideration Weiner et al. does not explicitly teach the limitation "from the same species as the non-IgE protein" recited in claim 1.

4. Previous rejection of claims 1, 14, 16, 17, 19, 21, 22, 54-56, 58-62, 65-67, 69-73, 74 and 76 under 35 U.S.C. 102(b) as being anticipated by Yang et al. (Yang et al., Induction of potent

Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999). J Infect Dis. 184(7):809-16, 2001) is **withdrawn** because upon further consideration Yang et al. (2001) does not explicitly teach the limitation "from the same species as the non-IgE protein" recited in claim 1.

5. Previous rejection of claims 1, 14, 16, 17, 19, 21, 22, 54-56, 58-62, 65-67, 69-73, 74 and 76 remain rejected under 35 U.S.C. 102(b) as being anticipated by Yang et al. (Yang et al., Induction of inflammation by West Nile virus capsid through the caspase-9 apoptotic pathway. Emerg Infect Dis. 8(12):1379-84, 2002) is **withdrawn** because upon further consideration Yang et al. (2002) does not explicitly teach the limitation "from the same species as the non-IgE protein" recited in claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Previous rejection of claims 1 and 77 under 35 U.S.C. 103(a) as being unpatentable over **Yang et al.** (Yang et al., Induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999). J Infect Dis. 184(7):809-16, 2001) in view **Letvin et al.** (WO 99/16466, international publication date 04/08/1999) is **withdrawn** replaced by the following 103 rejections upon further consideration.

The following new grounds of 103 rejections are made of record upon further *consideration of Applicant's arguments filed on 03/22/2010* and on 06/22/2010.

7. Claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Yang et al.** (Yang et al., Induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999). J Infect Dis. 184(7):809-16, 2001) in view **Letvin et al.** (WO 99/16466, international publication date 04/08/1999) and **Levinson et al.** (US 2006/0052592, publication date 03/09/2006, PCT/US03/19383 filed on 06/20/2003, provisional application No: 60/390,304 filed on 06/20/2002) and **Meazza et al.** (Meazza et al., Expression of two interleukin-15 mRNA isoforms in human tumors does not correlate with secretion: role of different signal peptides, Eur J Immunol. 27(5):1049-54, 1997; this reference has been cited by Applicant in the IDS filed on 08/31/2010).

Claim 1 filed on 11/12/2010 is directed to an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: (i) a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and (ii) a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating cytokine.

Claim 14 is directed to the isolated nucleic acid molecule of claim 1 wherein said isolated nucleic acid molecule is a plasmid.

Claim 16 is directed to a composition comprising a nucleic acid molecule of claim 1 and a nucleic acid molecule that comprises a nucleic acid sequence that encodes an immunogen.

Claim 17 is directed to the composition of claim 16 wherein said composition comprises a nucleic acid molecule that encodes an immunogen, wherein said immunogen is a

pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases.

Claim 19 is directed to the composition of claim 17 wherein said immunogen is a pathogen antigen is from a pathogen selected from the group consisting of HIV, HSV, HCV, and WNV.

Claim 55 is directed to the isolated nucleic acid molecule of claim 1 comprising a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein.

Claim 56 is directed to the isolated nucleic acid molecule of claim 55 wherein said isolated nucleic acid molecule is a plasmid.

Claim 58 is directed to a composition comprising a nucleic acid molecule of claim 55 and a nucleic acid molecule that comprises a nucleic acid sequence that encodes an immunogen.

Claim 59 is directed to the composition of claim 58 wherein said composition comprises a nucleic acid molecule that encodes an immunogen, wherein said immunogen is a pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases.

Claim 60 is directed to the composition of claim 59 wherein said immunogen is a pathogen antigen is from a pathogen selected from the group consisting of HIV, HSV, HCV, and WNV.

Claim 66 is directed to the isolated nucleic acid molecule of claim 1 comprising a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide wherein the non-IgE protein is an immunomodulating protein.

Claim 67 is directed to the isolated nucleic acid molecule of claim 66 wherein said isolated nucleic acid molecule is a plasmid.

Claim 69 is directed to a composition comprising a nucleic acid molecule of claim 66 and a nucleic acid molecule that comprises a nucleic acid sequence that encodes an immunogen.

Claim 70 is directed to the composition of claim 69 wherein said composition comprises a nucleic acid molecule that encodes an immunogen, wherein said immunogen is a

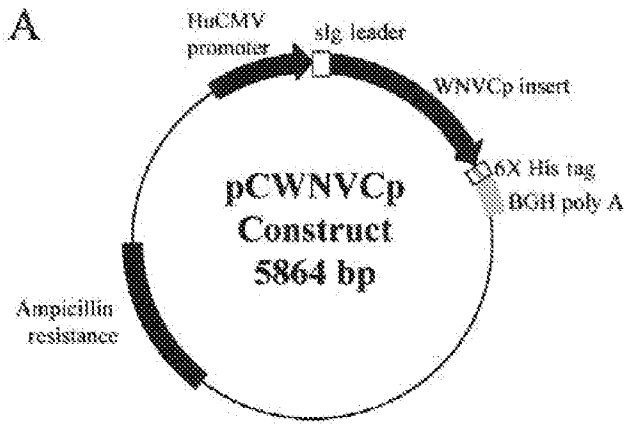
pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases.

Claim 71 is directed to the composition of claim 70 wherein said immunogen is a pathogen antigen is from a pathogen selected from the group consisting of HIV, HSV, HCV, and WNV.

Claim 77 is directed to the isolated nucleic acid molecule of claim 1, wherein the non-IgE protein is an immunomodulating protein IL-15.

Claim interpretation: **(I)** It is noted that the limitation "a nucleic acid sequence selected from the group consisting of" clearly indicates that the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" and the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof" are two different species that can be selected from to be the claimed "isolated nucleic acid". In other words, the art is required to discloses either the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" or the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof". **(II)** In the absence any peptide sequence encoded by a nucleic acid sequence disclosed in specification and/or recited in the claims, the limitation "an IgE signal peptide" encompass any variant of signal peptide of an immunoglobulin E (IgE).

With regard to claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77, Yang et al. teaches induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999) (See title, Yang et al., 2001). Yang et al. teaches that West Nile virus (WNV) is a vectorborne pathogen that induces brain inflammation and death. Recently, confirmed cases of infection and deaths have occurred in the United States Mid-Atlantic region. Yang et al. teaches a DNA vaccine encoding the WNV capsid protein was constructed, and the in vivo immune responses generated were investigated in DNA vaccine-immunized mice. Antigen-specific humoral and cellular immune responses were observed, including a potent induction of antigen-specific Th1 and cytotoxic T lymphocyte responses. Strong induction of Th1-type immune responses included high levels of antigen-specific elaboration of the Th1-type **cytokines** interferon-gamma and interleukin-2 and beta-chemokines RANTES (regulated upon activation, normal T cell-expressed and secreted) and macrophage inflammatory protein-1beta. Dramatic infiltration of CD4 and CD8 T cells and macrophages also was observed at the muscle injection site. Yang et al. states that these results support the potential utility of this method as a tool for developing immunization strategies for WNV and other emerging pathogens (See abstract, Yang et al., 2001). Furthermore, Yang et al. teaches a recombinant DNA vaccine, a plasmid construct, as a composition comprises a nucleic acid sequence encoding the human immunoglobulin secretory leader signal (See sIg leader, indicated in Figure 1A, page 810, Yang et al., 2001, and the plasmid map provided below) fused West Nile Virus (WNV) capsid protein (Cp).



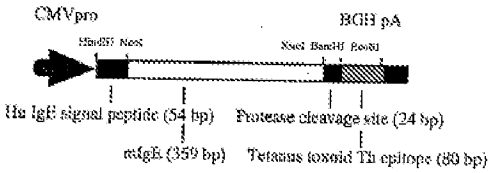
Yang et al. does not explicitly teach **(i)** the limitation "from the same species as the non-IgE protein" recited in claims 1 and 55, and **(ii)** the limitation the immunomodulating protein is a cytokine recited in claim 1 and the limitation the non-IgE protein is an immunomodulating protein is IL-15 recited in claim 77, **(iii)** the limitation "IgE signal peptide" recited in claims 1, 55 and 66.

With regard to **(i)** the limitation "from the same species as the non-IgE protein" recited in claims 1 and 55, and **(ii)** the limitation the immunomodulating protein is a cytokine recited in claim 1 and the limitation the non-IgE protein is an immunomodulating protein is IL-15 recited in claim 77, **Letvin et al.** (WO 99/16466) teaches a vaccine composition having a mammalian cytokine fusion protein (e. g., murine or human) or a homologue or analogous protein thereof, as described herein. Accordingly, the claimed invention embodies a vaccine composition having the nucleic acid sequence (e. g., SEQ ID NO : 1 or 3) that codes for a cytokine fusion protein. The vaccine composition also comprises the cytokine fusion protein comprising the amino acid sequence of SEQ ID NO: 2 or 4, or an amino acid sequence encoded by SEQ ID NO : 1 or 3, or a homolog thereof (See for instance, lines 3-10 of page 14, Letvin et al., 1999). Letvin et al.

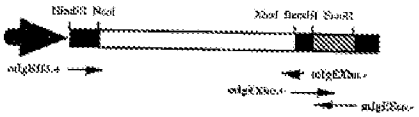
teaches the immunologic effects of co-administering protein and plasmid cytokines with an HIV-1 gpl20 DNA vaccine in mice. Administering plasmid cytokines before or with gpl20 DNA decreased gpl20-specific antibody titers and T cell functional activity, whereas administering plasmid cytokines after gpl20 DNA augmented gpl20-specific immune responses. These results demonstrate that antigen-cytokine timing is a critical parameter in determining the overall biologic effect of the cytokine. Moreover, IL-2/Ig was significantly more effective than IL-2 in augmenting DNA vaccine-elicited immune responses, indicating that the Ig fusion markedly enhances the adjuvant properties of this cytokine (See for instance, lines 3-10 of page 18, Letvin et al., 1999). Letvin et al. teaches the use of plasmid-expressed cytokines as a strategy for **augmenting** immune responses elicited by plasmid DNA vaccines and the cytokine may be e.g. IL-2, GM-CSF, IL-4, IL-6, IL-7, IL-13, IL-10, IL-12, **IL-15**, TNF-alpha or IFN-gamma (See for instance, lines 14-18 of page 11, lines 20-29 of page 18, and Example 13 on pages 35-36, Letvin et al., 1999).

With regard to **(iii)** the limitation "IgE signal peptide" recited in claims 1, 55 and 66, **Levinson et al.** teaches human IgE signal peptide in the construction and in vitro expression of human IgE tetanus fusion protein (See Figure 2, Levinson et al., US 2006/0052592, shown below, which is also disclosed in Figure 2 of provisional application No: 60/390,304 filed on 06/20/2002).

A. Human mIgE - Tetanus toxoid fusion protein expression cassette



B. PCR amplification with specific primer set



With regard to IL-15 recited in claim 77 and the endogenous signal peptide present in human IL-15, **Meazza et al.** teaches that Interleukin (1L)-15 is a four-helix bundle cytokine sharing several biological properties with IL-2. By reverse transcriptase-polymerase chain reaction analysis, human cancer cell lines of different histotypes are shown to express two IL-15 amplification products: a 524-bp band corresponding to the IL-15 mRNA found in macrophages, and another of 643 bp corresponding to an alternatively spliced mRNA including a 119-bp alternative exon. IL-15 was undetectable in the supernatant of tumor cell lines expressing either one or both of the mRNA isoforms as evaluated by a bioassay or by ELISA, indicating that IL-15 is not secreted. However, IL-15 could be detected intracellularly in some tumor cells by confocal microscopy analysis. Since the pre-proteins encoded by the two mRNA isoforms differ in the signal peptide sequence, we have analyzed the characteristics of these signal peptides and their possible role in controlling secretion. The two IL-15 cDNA isoforms, expressed in COS-7 cells, induced very low levels of IL-15 secretion. However, substitution of the sequence encoding natural signal peptide(s) with the one from IgVx chain in the IL-15 cDNA results in a

significantly higher secretion of biologically active IL-15 (15-30-fold) upon cDNA transfection. A poor efficiency of natural signal peptides may represent one of the mechanisms involved in the control of IL-15 secretion (See abstract, Fig. 4 shown below, Meazza et al., 1997).

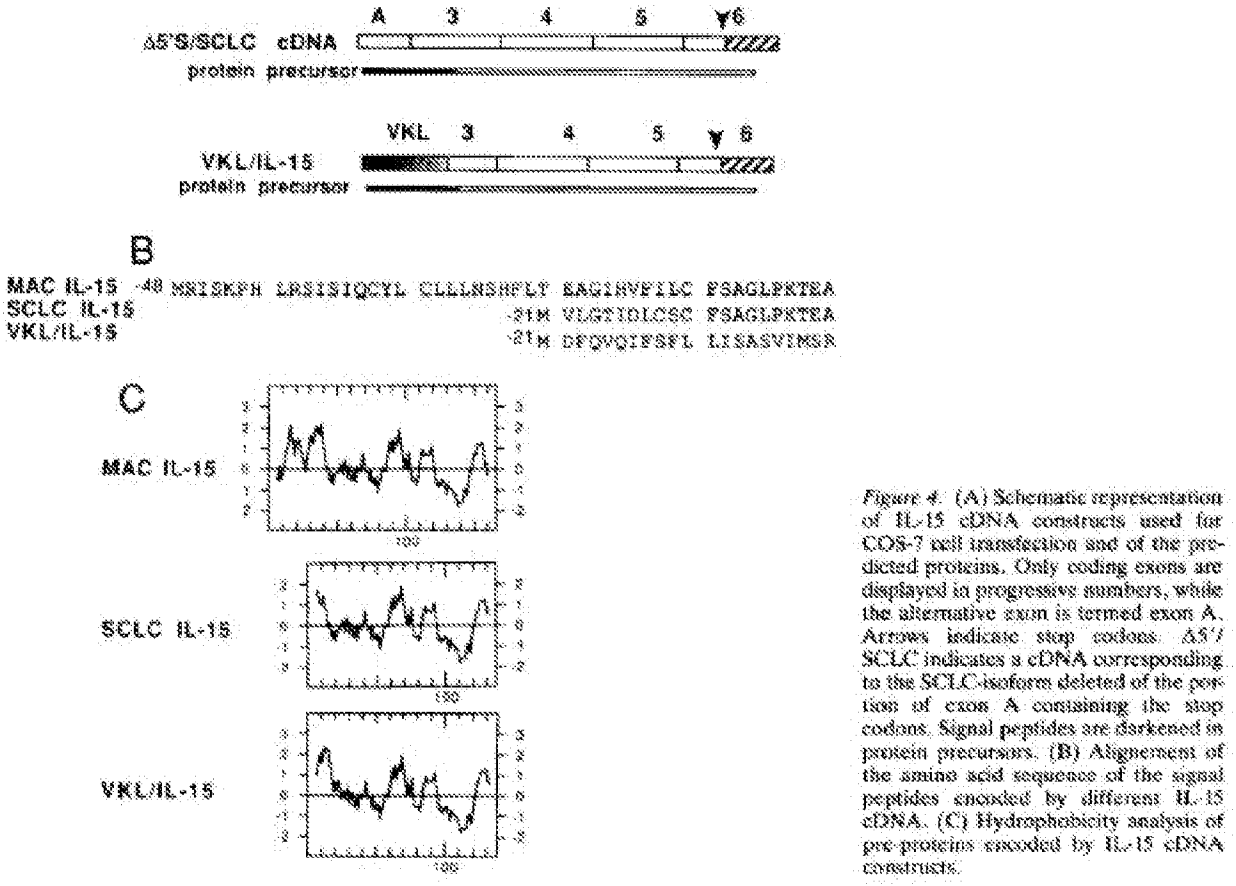


Figure 4. (A) Schematic representation of IL-15 cDNA constructs used for COS-7 cell transfection and of the predicted proteins. Only coding exons are displayed in progressive numbers, while the alternative exon is termed exon A. Arrows indicate stop codons. Δ5'/ SCLC indicates a cDNA corresponding to the SCLC-isoform deleted of the portion of exon A containing the stop codons. Signal peptides are darkened in protein precursors. (B) Alignement of the amino acid sequence of the signal peptides encoded by different IL-15 cDNA. (C) Hydrophobicity analysis of pre-proteins encoded by IL-15 cDNA constructs.

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Yang et al. regarding a recombinant DNA vaccine, a plasmid construct, as a pharmaceutical composition comprises a nucleic acid sequence encoding the human immunoglobulin secretory leader signal (See sIg leader, indicated in Figure 1A, Yang et al., 2001, and the plasmid map provided below) fused West Nile Virus (WNV) capsid protein (Cp), with the teachings of (i) Letvin et al. regarding the use of plasmid-expressed human cytokine IL-15 as a strategy for augmenting immune responses elicited by

plasmid DNA vaccines, (ii) Levinson et al. regarding human IgE signal peptide in the construction and in vitro expression of human IgE tetanus fusion protein, and (iii) Meazza et al. regarding substitution of the sequence encoding natural human IL-15 signal peptide(s) with the signal peptide from IgVx chain in the IL-15 cDNA results in a significantly higher secretion of biologically active IL-15 upon cDNA transfection, to arrive at isolated nucleic acid recited in claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77 of instant application by substitution of WNVCp encoding sequences taught by Yang et al. with IL-15 coding sequence and fused to either sIg leader taught by Yang et al. or fused to human IgE signal peptide taught by Levinson et al. for expression of human IL-15 with desired secretion level taught by Meazza et al., in the context of the plasmid taught by either Yang et al. (2001) or Letvin et al. (1999).

One having ordinary skill in the art would have been motivated to combine the teachings of Yang et al., Letvin et al., Levinson et al., and Meazza et al. because (i) Letvin et al. specifically teaches the expression of cytokines, including IL-15 and IL-2, as a strategy for augmenting immune responses elicited by plasmid DNA vaccines, (ii) Levinson et al. teaches human IgE signal peptide in the construction and in vitro expression of human IgE-tetanus fusion protein, and (iii) Meazza teaches substitution of the sequence encoding natural human IL-15 signal peptide(s) with the signal peptide from IgVx chain in the IL-15 cDNA results in a significantly higher secretion of biologically active IL-15 upon cDNA transfection. The combined teachings of Yang et al., Letvin et al., Levinson et al., and Meazza et al. demonstrate using an IgE signal peptide for expression of a non-IgE protein, such as human cytokine IL-15, at a desired secretion level from an isolated nucleic acid molecule, such as a DNA vaccine.

There would have been a reasonable expectation of success given (i) successful demonstration of the induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999) and release of various cytokines by T-cells of immunized mice, by the teachings Yang et al. (See Figure 3, Yang et al., 2001), (ii) successful demonstration of IL-2/Ig fusion protein in enhancement of antigp120 immune response elicited by pV1-gp120, by the teachings of Letvin et al. (See Example 8, pages 26-29), and (iii) successful demonstration of human IgE signal peptide in the construction and in vitro expression of human IgE tetanus fusion protein, by the teachings of Levinson et al., and (iv) successful demonstration of substitution of the sequence encoding natural human IL-15 signal peptide(s) with the signal peptide from IgVx chain in the IL-15 cDNA results in a significantly higher secretion of biologically active IL-15 upon cDNA transfection, by the teachings of Meazza et al.

Thus, the claimed invention as a whole was clearly prima facie obvious

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) [available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf; and KSR Guidelines Update has been published in the Federal Register at 75 Fed. Reg. 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at http://www.uspto.gov/patents/law/notices/2010.jsp]. The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc., the suggestion and motivation to combine Yang

et al., Letvin et al., Levinson et al. and Meazza et al. has been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's arguments

Applicant argues that IL-15 comprises its own signal peptide. Nothing in Yang 1 or Letvin would suggest linking IL-15 to a non-IL-15 signal peptide in view of the existence of its own IL-15 signal peptide. Yang 1 provides a human signal peptide to the viral protein West Nile virus capsid protein in order to provide it with a signal peptide to enhance its expression. IL- 15 already includes a signal peptide and one skilled in the art would not see any benefit to add a second signal peptide or use an IgE signal peptide in its place. Applicant states that one skilled in the art viewing the prior art would not consider the claimed invention obvious. The elected species of the claims invention provides coding sequences for a fusion protein that comprises an IgE signal peptide linked to IL-15 coding sequences. Applicant states that to combine Yang 1 and Letvin to produce the claimed invention as suggested in the Office Action, one skilled in the art would insert the IL-15 coding sequences in place of the West Nile Virus capsid protein sequence. The resulting construct however would comprise an IgE signal peptide linked to an IL-15 protein that contains its own signal peptide. One skilled in the art would not produce such a construct because one skilled in the art would not include two signal peptides in view of the combined teachings. Such a construct is not obvious (See page 16 of Applicant's remarks filed on 03/22/2010).

Applicant argues that the Office asserts that it would be obvious to exchange the WNV capsid encoding sequences with IL-15 encoding sequences taught by Letvin. This is incorrect. First, doing so destroys the purpose of Yang 2001 which is to induce anti-WNV capsid specific immune responses. Second, Letvin teaches using an IL-15 signal peptide and that immunomodulatory proteins to boost immunity. Combining it with Yang as asserted by the

Office requires using a protein that boosts immunity in place of the protein against which immunity is sought (See pages 3-4 of Applicant's remarks filed on 06/22/2010)

Response to Applicant's arguments

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above.

It is noted that **Yang et al.** teaches a recombinant DNA vaccine, a plasmid construct, as a composition comprises a nucleic acid sequence encoding the human immunoglobulin secretory leader signal. **Levinson et al.** teaches human IgE signal peptide in the construction and in vitro expression of human IgE tetanus fusion protein (See Figure 2, shown below, Levinson et al., provisional application No: 60/390,304 filed on 06/20/2002). Therefore, using "human IgE signal peptide" to express a non-IgE protein is clearly taught by Yang et al and Levinson et al. With regard to a given non-IgE protein, including cytokine IL-15, to be expressed in the fusion protein, **Meazza et al.** teaches substitution of the sequence encoding natural signal peptide(s) with the one from IgVx chain in the IL-15 cDNA results in a significantly higher secretion of biologically active IL-15 (15-30-fold) upon cDNA transfection.

It is worth noting that the claims of instant application does not require any specific limitation regarding exclusion of endogenous signal peptide that may be present in a given non-IgE protein, and there is no requirement for specific biological activity of the fusion non-IgE protein with IgE signal peptide. When a signal peptide is present in a given non-IgE protein that render poor secretion, the secretion level of the non-IgE fusion protein can be enhanced by substituting the endogenous signal peptide with a IgE signal peptide when a high level of secretion of the non-IgE fusion protein is desired.

With regard to the role of cytokine in induction of immune response by a DNA vaccine, **Yang et al.** teaches a DNA vaccine encoding the WNV capsid protein was constructed, and the in vivo immune responses generated were investigated in DNA vaccine-immunized mice. Antigen-specific humoral and cellular immune responses were observed, including a potent induction of antigen-specific Th1 and cytotoxic T lymphocyte responses. Strong induction of Th1-type immune responses included high levels of antigen-specific elaboration of the Th1-type

cytokines interferon-gamma and interleukin-2 and beta-chemokines RANTES (regulated upon activation, normal T cell-expressed and secreted) and macrophage inflammatory protein-1beta. Furthermore, **Letvin et al.** teaches that administering plasmid cytokines after gpl20 DNA augmented gpl20-specific immune responses. Consistently, Letvin et al. teaches the use of plasmid-expressed cytokines as a strategy for **augmenting** immune responses elicited by plasmid DNA vaccines and the cytokine may be e.g. IL-2, GM-CSF, IL-4, IL-6, IL-7, IL-13, IL-10, IL-12, **IL-15**, TNF-alpha or IFN-gamma (See for instance, lines 14-18 of page 11, lines 20-29 of page 18, and Example 13 on pages 35-36, Letvin et al., 1999).

Therefore, Applicant's arguments "The Office asserts that it would be obvious to exchange the WNV capsid encoding sequences with IL-15 encoding sequences taught by Letvin. This is incorrect. First, doing so destroys the purpose of Yang 2001 which is to induce anti-WNV capsid specific immune responses. Second, Letvin teaches using an IL-15 signal peptide and that immunomodulatory proteins to boost immunity. Combining it with Yang as asserted by the Office requires using a protein that boosts immunity in place of the protein against which immunity is sought" have been fully considered and found not persuasive.

8. Claims 1, **15**, 55, **57**, 66, and **68** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Yang et al.** (Yang et al., Induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999). J Infect Dis. 184(7):809-16, 2001) in view **Letvin et al.** (WO 99/16466, international publication date 04/08/1999) and **Levinson et al.** (US 2006/0052592, publication date 03/09/2006, PCT/US03/19383 filed on 06/20/2003, provisional application No: 60/390,304 filed on 06/20/2002) and **Meazza et al.** (Meazza et al., Expression of two interleukin-15 mRNA isoforms in human tumors does not correlate with secretion: role of different signal peptides, Eur J Immunol. 27(5):1049-54, 1997; this reference has been cited by Applicant in the IDS filed on

08/31/2010), as applied to claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77 above, and further in view of **Aarts et al.** (Aarts et al., Vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, Cancer Res. 62(20):5770-7, 2002).

It is noted that claims 1, 55, and 66 are included in the rejection because claim **15** depends from claim 1, claim **57** depends from claims 1 and 55, and claim **68** depends from claims 1 and 66.

Claim 15 is directed to the nucleic acid molecule of claim 1 incorporated into a viral vector.

Claim 57 is directed to the nucleic acid molecule of claim 55 incorporated into a viral vector.

Claim 68 is directed to the nucleic acid molecule of claim 66 incorporated into a viral vector.

The teachings of Yang et al., Letvin et al., Levinson et al., and Meazza et al. have been discussed in the preceding section of the rejection of claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77 under 35 U.S.C. 103(a) as being unpatentable over Yang et al. in view of Letvin et al., Levinson et al., and Meazza et al.

None of Yang et al., Letvin et al., Levinson et al., and Meazza et al. explicitly teaches the limitation "a viral vector" recited in claims 15, 57, and 68.

With regard to the limitation "limitation "a viral vector" recited in claims 15, 57, and 68, **Aarts et al.** teaches vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity (See title and abstract, Aarts et al., 2002). Aarts et al. teaches various vaccination regimen starting with prime (i.e. initial)

administration of a composition comprising a nucleic acid encoding human tumor antigen, carcinoembryonic antigen (CEA), expressed from a recombinant vaccinia (rV) vector such that the host develops an immune response against human CEA, followed by multiple subsequent booster vaccinations, which comprise administration of recombinant cytokines including recombinant GM-CSF and IL-2 (See Materials and Methods, and Table 1, Aarts, et al., 2002).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Aarts et al. regarding using a viral vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, into the combined teachings of Yang et al., Letvin et al., Levinson et al., and Meazza et al. directed to an isolated plasmid nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: (i) a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and (ii) a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating cytokine, to arrive the claimed isolated nucleic acid recited in claims 15, 57, and 68 by substituting a plasmid taught by Yang et al., Letvin et al., and Levinson et al. with a viral vector taught by Aarts et al.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Aarts et al. into the combined teachings Yang et al., Letvin et al., Levinson et al., and Meazza et al. because Aarts et al. specifically teaches using viral vector for expression of cytokine from a DNA vaccine.

There would have been a reasonable expectation of success given (i) successful demonstration of the induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999) and release of various cytokines by T-cells of immunized mice, by the teachings Yang et al. (See Figure 3, Yang et al., 2001), (ii) successful demonstration of IL-2/Ig fusion protein in enhancement of antigp120 immune response elicited by pV1-gp120, by the teachings of Letvin et al. (See Example 8, pages 26-29), and (iii) successful demonstration of human IgE signal peptide in the construction and in vitro expression of human IgE tetanus fusion protein, by the teachings of Levinson et al., and (iv) successful demonstration of substitution of the sequence encoding natural human IL-15 signal peptide(s) with the signal peptide from IgVx chain in the IL-15 cDNA results in a significantly higher secretion of biologically active IL-15 (15-30-fold) upon cDNA transfection, by the teachings of Meazza et al., and (v) successful demonstration of expression of cytokine IL-2, GM-CSF enhance induction of immune response to an antigen expressed from a DNA vaccine, by the teachings of Aarts et al..

Thus, the claimed invention as a whole was clearly prima facie obvious

Conclusion

9. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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Art Unit 1632